Epidermal Growth Factor Receptor Mutation Status in Stage I Lung Adenocarcinoma with Different Image Patterns

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Purpose: Early lung adenocarcinoma may present with ground-glass opacity (GGO) component in computed tomography (CT) scan. Epidermal growth factor receptor (*EGFR*) mutation had been reported in patients with lung cancer with GGO patterns. Nevertheless, the correlation between clinical characteristics, CT image patterns, and *EGFR* mutation status was indeterminate.

Methods: Patients with stage I lung adenocarcinoma with tumor lesions less than 3 cm were included and classified into pure GGO, part-solid, and solid patterns by CT scan images. All patients had *EGFR* mutation test from frozen tumors. Available paraffin-embedded archival tissues were microdissected into three different locations similar to CT images with central and peripheral parts of tumor, and adjacent normal part for *EGFR* mutation tests.

Results: Totally, 162 patients were analyzed, 90 women and 72 men, and 128 nonsmokers. The patients included 35 (21.6%) pure GGO, 41 (25.3%) part-solid, and 86 (53.1%) solid lesions. The *EGFR* mutation rate was 64.2% ($n = 104$). Analysis of the correlation between CT image patterns and *EGFR* mutation, the less GGO ratio had more typical mutation, especially L858R ($p = 0.037$). In 45 microdissected tumors, the central and peripheral parts had the same *EGFR* mutation status. In adjacent normal parts, 5 of 32 (15.6%) *EGFR* mutant patients had identical mutation but none in nonmutant patients.

Conclusions: In stage I lung adenocarcinoma, typical mutation, especially L858R was detected more frequent in invasive solid pattern and significantly less in pure GGO pattern. *EGFR* mutation is an early event in the pathogenesis of lung adenocarcinoma and may facilitate the tumor into aggressive behavior.

Key Words: Non-small cell lung cancer, Epidermal growth factor receptor (*EGFR*), Ground-glass opacity.

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Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers, and the frequency of adenocarcinoma has increased recently.[1] Surgery remains the gold standard for stage I disease. Early detection is the main way to cure NSCLC. Because of improvement of computed tomography (CT) images with higher resolution and the increasing prevalence of low-dose CT screening for lung cancer detection, small and early NSCLCs are detected more frequently than before.[2,3] Small and early lung cancer lesions may present in CT scan as ground-glass opacity (GGO), part-solid, or solid patterns.[4] GGO is also a very common CT image pattern of NSCLC in Asian countries,[2] including Taiwan.

NSCLC is characterized by the accumulation of multiple genetic alterations that results from the inactivation of tumor suppressor genes, activation of oncogenes, and epigenetic changes. Epidermal growth factor receptor (*EGFR*), a transmembrane glycoprotein is involved in the cancer cell proliferation, angiogenesis, and resistance to apoptosis.[5,6] The *EGFR* is frequently overexpressed in NSCLC.[7,8] Somatic mutations in the *EGFR* gene have also been well documented as a major determinant of the clinical response to small molecule *EGFR* specific tyrosine kinase inhibitors, such as gefitinib or erlotinib.[9–11] The two most common *EGFR* mutations, exon 19 deletion and L858R in exon 21, represent 85 to 90% of *EGFR* mutations.[12] *EGFR* mutation had been reported in patients with lung cancer with GGO patterns, and these two typical *EGFR* mutations might determine the natural history of GGO lesions.[13]

In this study, we retrospectively surveyed the *EGFR* mutation status of patients with stage I lung adenocarcinoma ($n = 162$) with including criteria as lung tumor lesion less than 3 cm and adenocarcinoma (including bronchioloalveolar cell carcinoma [BAC]). The association of image patterns on CT scans and the *EGFR* mutation status in lung adenocarcinoma will be determined.

PATIENTS AND METHODS

Patients

Part of the patients was from an ongoing Taiwan national cooperative study—Genetic Epidemiologic Study of Lung Adenocarcinoma—aimed at understanding the causes of lung cancer, particularly lung adenocarcinoma, and the other patients were from Taichung Veterans General Hospital. All the patients underwent surgical resection from January 2001 to March 2009. The lung tumor lesions were completely resected with lymph node dissection. This study was approved by the Joint Institutional Review Board of Taiwan and the Institutional Review Board of Taichung Veterans General Hospital. The pathological diagnoses were based on the 2004 World Health Organization histologic classification system.[14] Tumor, node, and metastases staging system was used according to the 6th edition of the American Joint Committee for Cancer staging system.[15] Clinical information including patient's age, gender, tumor location, tumor size, stage, smoking status (nonsmoking defined as patients had never smoked), the status of *EGFR* mutation, and CT image patterns of the lung cancer was collected for analysis.

The excluding criteria were (1) nonadenocarcinoma cell type, (2) pathological stages II, III, and IV, and (3) tumor size large than 3 cm.

Image Patterns

The patients were divided into three groups such as pure GGO, part-solid, and solid patterns according to the images over the CT scanning. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures. The tumor contents were classified according to the extent occupied by GGO within the whole tumor. Tumor shadow disappearance rate (TDR) was used for presenting the GGO ratio.[16] The clinicians quantified the maximum dimension of the tumor (maxD) and the largest dimension perpendicular to the maximum axis (perD) on both lung and mediastinal windows. As previously reported, TDR was defined as the following:

$$\text{TDR} = 1 - (\text{maxD} \times \text{perD on mediastinal windows}/\text{maxD} \times \text{perD on lung windows})$$

After modification from the study by Chung et al.,[17] the tumors were then classified into three patterns according to the TDR. The first one was pure GGO pattern, which mean there was no solid component in the tumor, and the TDR was 1 (Supplementary Figure S1A, http://links.lww.com/JTO/A83). The second one was part-solid pattern, which mean only a few solid component in the tumor, and the TDR was large than 0.5 (Supplementary Figure S1B, http://links.lww.com/JTO/A83). The third one was the solid pattern, which means most of tumor is solid content, and the TDR was less than 0.5.

DNA Extraction from Frozen Tumor Tissue for EGFR Mutation Test

The frozen lung cancer tissues were obtained at surgery, immediately snap frozen in liquid nitrogen, and stored until use. Tumor specimens were procured for *EGFR* gene mutational analysis with previous description.[18] Briefly, DNA was extracted from the tumors using a QIAmp DNA Mini kit (Qiagen, Valencia, CA) following the manufacturer's protocols. The tyrosine kinase domain of the *EGFR* coding sequence, exons 18, 19, 20, and 21, was amplified by polymerase chain reaction and sequenced bidirectionally with an ABI Prism 3730 DNA Analyzer following standard protocol.

DNA Extraction from Microdissected Paraffin-Embedded Tissue for EGFR Mutation Test

Hematoxylin and eosin-stained sections of the available archived pathology specimens were reviewed by the pathologists (Y.-C.Y. and T.-Y.C.). For tumors with part solid and solid patterns, the central "solid" and peripheral "GGO" parts of the tumor, and the adjacent nontumor lung tissue were dissected under microscopy from paraffin-embedded tissues for *EGFR* mutation test. For tumors with purely GGO pattern radiologically, the central and peripheral parts of the tumor were microdissected separately. Finally, the microdissected specimens were obtained from three different locations (central part of tumor, peripheral part of the tumor, and the adjacent normal part) similar to the CT scan images.

Statistical Analysis

Categorical variables or continuous variables were analyzed by χ^2 tests, except where a small size (<5) required the use of Fisher's exact test or Student's t test, respectively. For multivariate analysis, multiple logistic regression with stepwise selection method was carried out to select significant variables. All reported p values were two sided, and a p value less than 0.05 was considered as statistically significant. All statistical analyses were performed using the SAS software (version 13.0; SAS Inc., Chicago, IL).

TABLE 1. Summary of Clinical Factors and *EGFR* Mutation Status of the Patients

Variables	*N* (*n* = 162) (%)
Gender	
Male	72 (44.4)
Female	90 (55.6)
Age, median (range)	59 (34–84)
Smoking status	
Nonsmoker	128 (79.0)
Exsmoker	16 (9.9)
Current smoker	18 (11.1)
Primary tumor location	
RUL	64 (39.5)
RML	11 (6.8)
RLL	25 (15.4)
LUL	46 (28.4)
LLL	16 (9.9)
Stage	
IA	100 (61.7)
IB	62 (38.3)
EGFR mutation status	
Wild type	58 (35.8)
L858R	47 (29.0)
Exon19 deletion	42 (25.9)
Others	15 (9.3)
Image patterns	
Pure GGO pattern	35 (21.6)
Part-solid pattern	41 (25.3)
Solid pattern	86 (53.1)

EGFR, epidermal growth factor receptor; GGO, ground-glass opacity.

RESULTS

Patients, Clinical Features, and EGFR Mutation Status

Totally, 162 patients were included in this study. Six of them were BAC (6/162, 3.7%). All the six patients had pure GGO patterns. The clinical factors and *EGFR* mutation status are presented in Table 1. The median age was 59 years (range: from 34 to 84 years). Female patients ($n = 90$, 55.6%) and nonsmokers ($n = 128$, 79%) were predominant in this study. Majority of tumor lesion (68%) was located at upper lobes. Pure GGO pattern represented 21.6% ($n = 35$), part-solid pattern 25.3% ($n = 41$), and solid pattern 53.1% ($n = 86$). The *EGFR* mutation rate was 64.2% ($n = 104$), 42 cases with exon 19 deletion (25.9%), 47 cases with L858R point mutation (29.0%), and 15 cases (9.3%) were other types.

CT Image Patterns, Clinical Features, and EGFR Mutation

According to the *EGFR* mutation status, female, nonsmoker had significantly more L858R point mutation compared with wild type ($p = 0.017$ and 0.035, respectively). The exon 19 deletions were significantly present more in nonsmoker group ($p = 0.006$) (Table 2).

The associations between clinical factors, *EGFR* mutation status, and CT image patterns were presented in Table 3.

TABLE 2. Association between Clinical Factors and *EGFR* Mutation Status with Wild Type, L858R, and Exon 19 Deletion[a]

Variables	Wild Type (%) (*n* = 58)	L858R (%) (*n* = 47)	Exon 19 Deletion (%) (*n* = 42)	*p*1[b]	*p*2[c]
Age (yr)[d]					
<59	30 (51.7)	16 (34.0)	20 (47.6)	0.069	0.685
≥59	28 (48.3)	31 (66.0)	22 (52.4)		
Gender					
Male	32 (55.2)	15 (31.9)	19 (45.2)	0.017	0.327
female	26 (44.8)	32 (68.1)	23 (54.8)		
Smoking status					
Nonsmoker	39 (67.2)	40 (85.1)	38 (90.5)	0.035	0.006
Exsmoker and current smoker	19 (32.8)	7 (14.9)	4 (9.5)		
Tumor size					
<20 mm	33 (56.9)	24 (51.1)	22 (52.4)	0.551	0.654
≥20 mm	25 (43.1)	23 (48.9)	20 (47.6)		

[a] *p* values were calculated by χ^2 test.
[b] *p*1 denotes the *p* values compared of wild type and L858R.
[c] *p*2 denotes the *p* values compared of wild type and exon 19 deletion.
[d] Age was divided to two groups according to median age.
EGFR, epidermal growth factor receptor.

TABLE 3. Association between Clinical Factors with *EGFR* Mutation Status Added and CT Image Patterns

Variables	Pure GGO (*n* = 30), *N* (%)	Part Solid (*n* = 37), *N* (%)	Solid (*n* = 80), *N* (%)	*p*
Age (yr)				
<59	15 (50.0)	24 (64.9)	27 (33.8)	0.006
≥59	15 (50.0)	13 (35.1)	53 (66.2)	
Gender				
Male	10 (33.3)	19 (51.4)	37 (46.3)	0.316
female	20 (66.7)	18 (48.6)	43 (53.7)	
Smoking status				
Nonsmoker	25 (83.3)	29 (78.4)	63 (78.8)	0.849
Exsmoker and current smoker	5 (16.7)	8 (21.6)	17 (21.2)	
Tumor size				
<20 mm	29 (96.7)	23 (62.2)	27 (33.8)	<0.0001
≥20 mm	1 (3.3)	14 (37.8)	53 (66.2)	
Mutation status				
Wild type	18 (60.0)	12 (32.4)	28 (35.0)	0.035
Typical mutation[c]	12 (40.0)	25 (67.6)	52 (65.0)	

[a] χ^2 test.
[b] The *p* values derived were between pure GGO versus part solid and solid patterns.
[c] Typical mutation denotes L858R and exon19 deletion.
EGFR, epidermal growth factor receptor; GGO, ground-glass opacity; CT, computed tomography.

The results showed that age ($p = 0.006$), tumor size ($p < 0.0001$), and *EGFR* mutation status ($p = 0.035$) were significantly associated with CT image patterns. According to the CT image patterns, patients older than 59 years had more

TABLE 4. Trend Test for the Proportion of *EGFR* Mutation Status among Different Image Patterns

Variables	Wild Type (%)	L858R (%)	Exon 19 Deletion (%)	$p1^a$	$p2^b$
All patients					
Image patterns	$n = 58$	$n = 47$	$n = 42$		
Pure GGO	18 (31.0)	5 (10.6)	7 (16.7)	0.024	0.272
Part solid	12 (20.7)	12 (25.5)	13 (31.0)		
Solid	28 (48.3)	30 (63.9)	22 (52.3)		
Stratified by gender					
Male	$n = 32$	$n = 15$	$n = 19$		
Pure GGO	7 (21.9)	0 (0.0)	3 (15.8)	0.334	0.482
Part solid	8 (25.0)	7 (46.7)	4 (21.1)		
Solid	17 (53.1)	8 (53.3)	12 (63.1)		
Female	$n = 26$	$n = 32$	$n = 23$		
Pure GGO	11 (42.3)	5 (15.6)	4 (17.4)	0.021	0.283
Part solid	4 (15.4)	5 (15.6)	9 (39.1)		
Solid	11 (42.3)	22 (68.8)	10 (43.5)		
Stratified by smoking status					
Nonsmoker	$n = 39$	$n = 40$	$n = 38$		
Pure GGO	14 (35.9)	5 (12.5)	6 (15.8)	0.011	0.070
Part solid	9 (23.1)	9 (22.5)	11 (29.0)		
Solid	16 (41.0)	26 (65.0)	21 (55.2)		
Smoker	$n = 19$	$n = 7$	$n = 4$		
Pure GGO	4 (21.1)	0 (0.0)	1 (25.0)	0.648	0.347
Part solid	3 (15.8)	3 (42.9)	2 (50.0)		
Solid	12 (63.1)	4 (57.1)	1 (25.0)		
Stratified by diameter					
Diameter <20 mm	$n = 33$	$n = 24$	$n = 22$		
Pure GGO	18 (54.6)	5 (20.8)	6 (27.3)	0.004	0.090
Part solid	8 (24.2)	6 (25.0)	9 (40.9)		
Solid	7 (21.2)	13 (54.2)	7 (31.8)		
Diameter ≥20 mm	$n = 25$	$n = 23$	$n = 20$		
Pure GGO	0 (0.0)	0 (0.0)	1 (5.0)	0.390	0.317
Part solid	4 (16.0)	6 (26.1)	4 (20.0)		
Solid	21 (84.0)	17 (73.9)	15 (75.0)		

[a] $p1$ denotes the p values compared of wild type and L858R.
[b] $p2$ denotes the p values compared of wild type and deletion.
EGFR, epidermal growth factor receptor; GGO, ground-glass opacity.

solid pattern and less number of pure GGO or part-solid pattern. In addition, the patients with tumor diameter large than 2 cm and typical *EGFR* mutation had significantly less number in pure GGO pattern than other types. The patients with part-solid or solid pattern had more typical *EGFR* mutation.

Further analysis was performed with trend test for the proportion of *EGFR* mutation status among different image patterns. Solid pattern had trend association with L858 point mutation ($p = 0.024$), but the trend association was not obtained in the exon 19 deletion ($p = 0.272$) although there was a tendency (Table 4). To explore the interaction of CT image patterns and *EGFR* mutation status in clinical covariates including gender, smoking status, and tumor diameter, the stratified analysis approach was performed. The significant trend association was only obtained in female ($p = 0.021$), nonsmoker ($p = 0.011$), and tumor diameter less than 2 cm ($p = 0.004$) with L858R point mutation and solid pattern tumor. Nevertheless, the association was not present in the exon 19 deletion (Table 4).

In addition, the less GGO ratio significantly had more L858R point mutation ($p = 0.037$) (Figure 1*A*). If the tumor size was also considered, pure GGO pattern had a trend to be smaller size and had less *EGFR* mutation (Figure 1*B*).

The result of mutational pattern from the frozen non-microdissected tissues was confirmed by 45 microdissected tumor cells in formalin-fixed paraffin-embedded tissues. The central and peripheral parts of tumor had the same *EGFR* mutation status (Figure 2). One patient had both exon 19 deletion and T790M mutation without any previous treatment. *EGFR* mutations identical to the tumors were detected in the adjacent normal part in 5 of 32 (15.6%) patients with *EGFR* mutant adenocarcinoma but none in 13 patients without mutation in the tumors. In these five patients with *EGFR* mutation in the adjacent normal parts, there were three patients with L858R, one with exon 19 deletion, and one with exon 18 mutation (Supplementary Table S1, http://links.lww.com/JTO/A83).

DISCUSSION

The carcinogenesis of the development of lung adenocarcinoma is still unclear. Some authors propose that a stepwise progression occurs from atypical adenomatous hyperplasia (AAH) through BAC to invasive adenocarci-

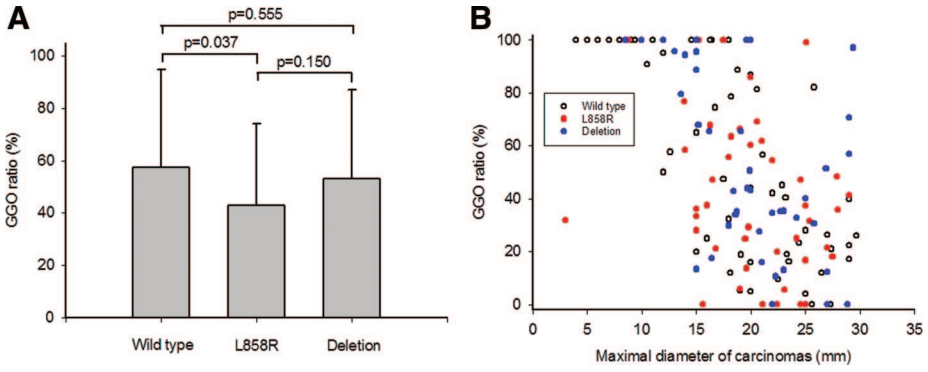

FIGURE 1. *A*, Ground-glass opacity (GGO) ratio and epidermal growth factor receptor (*EGFR*) mutation status. *B*, Relationship of the GGO ratio, tumor size, and *EGFR* mutation status.

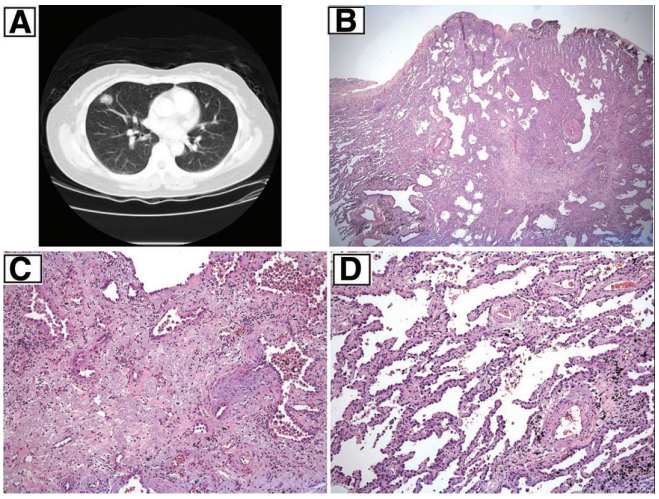

FIGURE 2. Computed tomography (CT) image and histopathology of the tumor. *A*, CT scan with a part-solid pattern lung adenocarcinoma over right lung and (*B*) the low-power histopathology of the tumor in hematoxylin and eosin (H&E) stain (×20). There are invasive carcinoma cells in the central part of tumor (*C*) and in situ carcinoma cells arranged in a bronchioloalveolar pattern in the periphery (*D*). Both the central and peripheral tumor parts have the same *EGFR* mutation status, L858R.

noma.[19,20] Nevertheless, it is still unknown how the lesion progresses over time in terms of radiological, pathological, and molecular characteristics.

BAC or early adenocarcinoma has three image patterns on CT scan included pure GGO, part solid, and solid.[21,22] These three image patterns correspond roughly to a biological range extending from benign lesions to invasive adenocarcinoma. The ratio of solid components usually related to disease progression.[19] Investigators have reported that the solid components in advanced-stage lesions are significantly larger than those in lesions at earlier stage.[19,23] Several investigators have suggested that the CT image patterns of small adenocarcinoma are closely related to the disease prognosis and that these features might be more important prognostic factors than are conventional considerations such as tumor size.[19,20,23,24] So lung cancer lesions with a solid component within the GGO nodule suggest increasing biological virulence, which mean that a solid component increases the level of suspicion for invasive adenocarcinoma.

EGFR mutations were detected in NSCLC and were more often seen in lung adenocarcinoma, particularly among Asians, females, and nonsmokers.[25–27] The incidence of *EGFR* mutation in lung adenocarcinoma in this study is very similar to the study in Asian patients[28] but higher than white patients.[29] The clinical implication of *EGFR* mutation is its close relationship to the patient's response to *EGFR* tyrosine kinase inhibitors.[9,10]

The relationship of GGO and *EGFR* was ever studied. Several studies have found a correlation between the *EFGR* mutation and BAC or BAC-like growth patterns.[30–33] Small peripheral adenocarcinoma or BAC may present with a high ratio of GGO components on CT scans. One would expect that GGO patterns may predict the presence of *EGFR* mutation, especially among female patients. In addition, L858R was more common in small size of tumor.[34] In the study of a clinicopathologic correlation between AAH, BAC, and *EGFR* mutation by Yoshida et al., *EGFR* mutations occur in the early stage of lung adenocarcinoma, such as AAH and BAC, suggesting that they might play an important role in disease progression. *EGFR* mutations are less frequently observed in AAH and BAC lesions compared with invasive adenocarcinoma.[35] Shigematsu et al.[27] studied *EGFR* mutation from seven pure BAC tumors out of 97 adenocarcinomas, and none of the seven tumors had *EGFR* TK domain mutations. Even though there were no statistically significant differences between *EGFR* TK domain mutation frequencies and the presence or percentage of BAC features ($p = 0.29$), the mean percentage with BAC feature with *EGFR* TK mutation was 30%, whereas it was 75% with negative *EGFR* TK domain mutation. Both studies showed that BAC might have less *EGFR* TK mutation than invasive adenocarcinoma.

In the study of correlation between *EGFR* mutation and GGO patterns, Yoshida et al.[13] found that *EGFR* mutations had little association with the progressive behavior of pure GGO. Glynn et al.[36] surveyed the association of the imaging characteristics with *EGFR* and *KRAS* mutations in patients with lung adenocarcinoma with BAC features. The presence of GGO on CT scan was not significantly associated with the presence of an *EGFR* mutation ($p = 0.44$). In five pure GGO patients with a high percentage of BAC (>75%), only one (20%) was positive for an *EGFR* mutation. Chung et al.[17] had a research on pathologic and radiologic correlation between *EGFR* mutation and multiple lung nodules with GGO patterns. According to the CT appearances, *EGFR* mutation was found in 38.4% of pure GGO lesions, 41.6% of mixed lesions, and 50% of solid GGO lesions. From these three researches, higher percentage of GGO had less *EGFR* TK domain mutation. This is compatible with our result.

In our study, *EGFR* mutation was detected less frequently in pure GGO lesions than in lesions with solid component, especially L858R. The invasive adenocarcinoma, such as tumors with part-solid and solid patterns, had higher incidence of *EGFR* mutation. That is, *EGFR* mutation may associate with the progression of tumor. In *EGFR* mutation analyses using microdissection, the central and the peripheral parts of tumor, and along with some of the adjacent nonneoplastic parts, always had the same *EGFR* mutation status. Our data suggested that the less invasive or noninvasive tumor parts presenting radiologically as peripheral GGO around central solid pattern had the same *EGFR* mutation status with the central invasive tumor part.

There are some possible explanations for the results. First, *EGFR* mutation was acquired in the relatively late stage in carcinogenesis of lung adenocarcinoma, and more invasive adenocarcinoma had more *EGFR* mutation. Nevertheless, this is against previous studies[13,35] and also our data from the microdissected tumors. Second, change in solid component was characterized by a significant rise in the incidence of allelic losses.[37] Different allelic loss patterns were found between the tumor cells in the central areas of alveolar

collapse or fibrosis and those in the peripheral region. The tumor cells in the central fibrotic areas have progressed to a more advanced stage than those in the peripheral regions. Third, lung tumors with *EGFR* mutation may progress more rapidly and develop into invasive cancer after combination with other genetic changes than those without mutations especially in central part of the tumor.

In our study, identical *EGFR* mutations in adjacent normal epithelium in 5 of 32 (15.6%) patients with *EGFR* mutant tumors suggest that the mutations occur as early events in the pathogenesis of these lung adenocarcinomas, starting from the histologically normal epitheliums. This finding suggested field effect phenomenon in lung adenocarcinoma and was also reported by Tang et al.[38] This finding may lead to clinical applications to target early detection and chemoprevention strategies. Nevertheless, even the central part and peripheral part of the tumor lesions harbored the same *EGFR* mutation status; the morphology patterns were different with more invasive component in central part of the tumors in part-solid and solid patterns. There must be involved with other genetic changes. Recent studies revealed that *EGFR* amplification commenced in the later stage of invasive adenocarcinoma.[39–43] Heterogeneous distribution of the *EGFR* amplification within individual tumors, especially the selective involvement in the invasive portions, supports an association with the invasive phenotype. In our study, part-solid and solid patterns had more *EGFR* mutation. *EGFR* mutation may involve the progression of the tumors through the combination of *EGFR* mutation and amplification and probably contributes to the switching to a tumor with a greater malignant potential. Other genes could also potentiate *EGFR* mutation in lung adenocarcinoma, such as inactivation of *P53* may be associated with the appearance of central consolidation.[13]

In our study, there were some differences between L858R and exon 19 deletions. L858R mutation is more likely to associate with female, and nonsmoker. Clinically, L858R mutation and exon 19 deletions have different presentation. Mitsudomi et al. found a correlation between *EGFR* genotype and response rate. In that study, patients with an exon 19 deletion showed a higher clinical response than *EGFR* point mutation. Nevertheless, it should be noted that the latter group included all point mutations and not just the L858R mutation.[44] Rosell et al. reported that a better response was associated with the exon 19 deletion than with the L858R mutation (odds ratio, 3.08; $p = 0.001$). In addition, the presence of the L858R mutation and the diagnosis of bronchioloalveolar adenocarcinoma were associated with poor prognosis compared with exon 19 deletion and adenocarcinoma in multivariate analyses.[29] Two reports compared the differences in survivals between patients with exon 19 deletions and with L858R mutations treated with gefitinib or erlotinib.[45,46] These data suggest that patients with an exon 19 deletions who are treated with gefitinib or erlotinib live longer than those with a L858R mutation. Nevertheless, it is possible that the mutation itself could have an effect on outcome. In our study, if lung adenocarcinoma harbors *EGFR* mutation, especially L858R, it may facilitate the tumor into more aggressive behavior and resulted into solid pattern.

In summary, in stage I lung adenocarcinoma with tumor size less than 3 cm, the part-solid and solid pattern tumors had more typical *EGFR* mutation. L858R point mutation was especially more frequent in invasive solid pattern. Pure GGO pattern tends to with tumor size less than 2 cm and has less typical *EGFR* mutation significantly, especially L858R. By microdissection, *EGFR* mutation status is the same in central and peripheral parts of the tumor, even in some adjacent normal epitheliums. *EGFR* mutation occurs as an early event in the pathogenesis of lung adenocarcinoma and may facilitate the tumor into more aggressive behavior. The difference between the typical *EGFR* mutations, L858R and exon 19 deletion, and their involvement in the process of lung adenocarcinoma formation needs further evaluation.

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